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CAS No. 71-55-6

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16. Abstracts

A bioassay for the possible carcinogenicity of technical grade 1,1,1-TRICHLOROETHANE was conducted using Osborne-Mendel rats and B6C3F1 mice. The 1,1,1-TRICHLOROETHANE was administered orally by gavage in corn oil to 50 animals of each sex and species at two dose levels 5 days per week for 78 weeks.

The rats received two doses of 1500 and 750 mg/kg which produced a moderate depression of body weight in the first year of the study. A yellow discoloration of lower abdominal fur, eye and nasal discharge and dyspnea were observed during the second year. Both male and female test animals exhibited early mortality. Surviving animals were killed at 117 weeks of age.

In mice, the doses were increased twice and the time-weighted average doses were 5,616 and 2,807 mg/kg. There was a moderate depression of body weight throughout the study

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16. Abstracts (Continued)

in both sexes and survival was significantly decreased.

Neoplasms encountered in both the treated and control animals had been seen previously in untreated animals. The neoplasms were not believed to be attributable to 1,1,1-TRICHLOROETHANE since no relationship was established between the dosage groups, species, sex, type of neoplasm or site of occurrence.

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BIOASSAY OF 1,1,1-TRICHLOROETHANE

FOR POSSIBLE CARCINOGENICITY

Carcinogen Bioassay and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause and Prevention
National Cancer Institute
Bethesda, Maryland

November 1976

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BIOASSAY OF 1,1,1-TRICHLOROETHANE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Program, Division of Cancer Cause and Prevention

National Cancer Institute

November 1976

CONTRIBUTORS: This report presents the results of the carcinogenesis bioassay conducted under the direction of the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. This research was conducted at Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Bioassay Program.

The results of this study were reviewed and this report was prepared at Tracor Jitco. Those responsible for the report are the toxicologists, Drs. W. E. MacDonald[2], and Jane F. Robens[2]; the technical editor, Dr. E. W. Gunberg[2]; and the technical writer, Ms. B. G. J. Rorts[2].

The experimental design, including doses, was determined by the NCI Project Officers, Drs. J. H. Weisburger[1,4] and E. K. Weisburger[1]. The principal investigators for the contract were Drs. M. B. Powers[3], R. W. Voelker[3], W. A. Olson[3,5], and W. M. Weatherholtz[3,6]. Chemical analysis was performed

by Dr. C. L. Guyton[3,7]; the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics[3].

The pathologic examinations were done by the Hazleton Laboratories America, Inc.[3], and the Experimental Pathology Laboratories[8]. The histopathologic evaluation was conducted by Dr. D. A. Willigan[9] and reviewed by Dr. C. N. Barron[2].

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute[10]; the statistical analysis was performed by Dr. J. R. Joiner[2], using methods selected for the Bioassay Program by Dr. J. J. Gart[11]. This report was reviewed by members of the participating organizations[1,2,3].

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SUMMARY

The carcinogenesis bioassay of technical grade 1,1,1-trichloroethane was conducted using Osborne-Mendel rats and B6C3F1 mice. 1,1,1-Trichloroethane was administered orally by gavage in corn oil to 50 animals of each sex and species at two dose levels 5 days per week for 78 weeks.

Rats: The experiment was originally started using doses of 3,000 and 1,500 mg/kg of body weight. After a few weeks the study was terminated, and the animals discarded because of marked signs of intoxication. The experiment was restarted with rats 7 weeks of age that were put on doses of 1,500 and 750 mg/kg. There was a moderate depression of body weight in the first year of the study. During the second year a yellow discoloration of the fur of the lower abdomen and increased eye and nasal discharge and dyspnea were noted. Both males and females given the test chemical exhibited early mortality when compared with the untreated controls, and the statistical test for dose-related trend was significant ($P < 0.04$). All surviving animals were killed at 117 weeks of age.

Mice: Male and female weanlings were started on test at 5 weeks of age and killed at 96 weeks of age. Initially, the doses for male and female mice were 4,000 and 2,000 mg/kg body weight. During the 10th week of the study, doses were increased to 5,000 and 2,500 mg/kg, since the animals apparently could tolerate a higher dose. Doses were again increased at week 20 to 6,000 and 3,000 mg/kg and maintained at these levels to the end of the study. Time-weighted average doses for the high- and low-dose mice were, respectively, 5,615 and 2,807 mg/kg. There was a moderate depression of body weight throughout the study in both sexes of mice, and the survival

was significantly decreased. In the female mice, there was a positive dose-related trend ($P = 0.002$) in the proportions surviving.

A variety of neoplasms were represented in both 1,1,1-trichloroethane-treated and matched-control rats and mice. However, each type of neoplasm has been encountered previously as a lesion in untreated rats or mice. The neoplasms observed are not believed attributable to 1,1,1-trichloroethane exposure, since no relationship was established between the dosage groups, the species, sex, type of neoplasm, or the site of occurrence. Even if such a relationship were inferred, it would be inappropriate to make an assessment of carcinogenicity of 1,1,1-trichloroethane on the basis of this test, because of the abbreviated life spans of both the rats and the mice.

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1.0 INTRODUCTION

1,1,1-Trichloroethane (commonly called methylchloroform) is one of a group of halogenated hydrocarbons selected for testing in the Carcinogenesis Bioassay Program. The rationale for its selection includes its structural relationship to carbon tetrachloride, its wide use in industry, its extensive exposure of humans, and the incomplete knowledge of its carcinogenic potential. In 1959 Browning reported that 1,1,1-trichloroethane was replacing the more toxic industrial solvents: trichloroethylene, tetrachloroethylene, and carbon tetrachloride. Furthermore a growing market has developed for 1,1,1-trichloroethane after reports suggested the carcinogenicity of carbon tetrachloride (Reuber and Glover, 1970; Della Porta et al., 1961; Eschenbrenner and Miller, 1946) and of trichloroethylene (National Cancer Institute, 1976). In the years 1970 through 1973, domestic sales grew from 327 to 566 million pounds (Chemical Economics Handbook, 1975). The Environmental Protection Agency permits 1,1,1-trichloroethane to be used as a solvent or cosolvent in pesticide formulations for the postharvest fumigation of citrus fruits (U.S. Environmental Protection Agency, 1972). The United States Occupational Standard requires that no worker be exposed to a concentration in excess of 350 ppm by volume, or 1,900 mg/m^3 determined as a time-weighted average exposure over an 8-hour workday (U.S. Dept of Labor, 1974).

2.0 MATERIALS AND METHODS

Chemicals

Two batches of technical grade 1,1,1-trichloroethane were purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The purity was checked by Hazleton Laboratories America, Inc., Vienna, Virginia, using gas-liquid chromatography (glc) and infrared spectrophotometry. Analyses by glc showed that both batches contained approximately 95% 1,1,1-trichloroethane and 3% p-dioxane, an inhibitor routinely added to commercial preparations of 1,1,1-trichloroethane. The remaining 2% of the glc peak area contained several minor impurities, two of which may have been 1,1-dichloroethane and 1,1-dichloroethylene. Throughout this report, the term 1,1,1-trichloroethane is used to represent the technical grade material.

Dosage Preparation

Fresh solutions of 1,1,1-trichloroethane in corn oil in amounts sufficient to dose all animals were prepared weekly, sealed, and refrigerated to reduce volatilization. The concentration of 1,1,1-trichloroethane in corn oil was 75% for rats and 40-60% for mice. Duke's® corn oil was purchased from a distributor, C. F. Sauer Co., Richmond, Virginia. Dosing was conducted under a hood to minimize extraneous exposure of other animals and laboratory personnel.

Animals

The Osborne-Mendel rat was selected because of the experience gained by the Food and Drug Administration, where this strain has been used for many

years as a general-purpose test animal. In addition, it was known to be sensitive to the carcinogenic effects of carbon tetrachloride administered by subcutaneous injection (Reuber and Glover, 1970). The B6C3F1 hybrid mouse was selected because it has been extensively used by NCI for carcinogenesis bioassays.

Rats and mice of both sexes, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these tests. The Osborne-Mendel rats, and the B6C3F1 hybrid mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, determined to be free from observable disease or parasites, and assigned to the various experimental and control groups.

Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. Incoming air was filtered through 2-inch-thick disposable fiberglass filters at a rate of 12 changes of room air per hour. Lighting was provided on a 12-hour-per-day cycle. Rats were individually housed in suspended steel, wire-mesh cages, and mice were in polypropylene cages equipped with filter tops. Ten mice were housed in each cage. Clean cages with bedding (Sanichips®, manufactured by Shurfire) were provided twice each week for mice; rats were given clean wire cages weekly.

Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Heat-sterilized glass water bottles were provided twice a week for rats and three times a week for mice. Food

(Wayne® Laboratory Blox Meal) and water were consumed ad libitum. Racks were repositioned in the room on a weekly basis.

Housed in the same room with the rats given 1,1,1-trichloroethane, were rats treated with trichloronitromethane, and trichlorofluoromethane; the matched controls for 1,1,1-trichloroethane and trichlorofluoromethane; and the vehicle controls for trichloronitromethane.

The 1,1,1-trichloroethane-treated mice were maintained in the same room as mice receiving 1,1,2,2-tetrachloroethane, trichloromethane, 3-chloro-1-propene, trichloronitromethane, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, 1,2-dichloroethane, 1,1-dichloroethane, trichloroethene, 2,5-dihydrothiophene 1,1-dioxide, triiodomethane, 1,1,2-trichloroethane, tetrachloroethene, hexachloroethane, carbon disulfide, trichlorofluoromethane, and tetrachloromethane (carbon tetrachloride). The control mice to these 17 chemicals were also housed in the same room as the 1,1,1-trichloroethane-treated mice.

Subchronic Toxicitity Tests

Subchronic toxicity studies were conducted to establish the maximum tolerated doses (MTD) of 1,1,1-trichloroethane for administration to the rats and mice in the chronic study. On the basis of results from the range-finding study, doses of 1,000, 1,780, 3,160, 5,620, and 10,000 mg/kg were administered in corn oil by gavage to five animals of each sex and species. Animals were dosed 5 days a week for 6 weeks, followed by 2 weeks of observation.

At 3,160 mg/kg none of the rats died and there was no reduction of weight

gain, while at 5,620 mg/kg, two female rats died and weight gain in the surviving females was reduced. At 10,000 mg/kg, two male rats died and weight gain in the survivors was reduced. The high dose for rats in the chronic study was therefore set at 3,000 mg/kg; the low dose was half that amount, or 1,500 mg/kg. No gross pathology was observed in rats at necropsy in the subchronic tests.

At 5,620 mg/kg none of the mice died and none had reduced weight gain, whereas at 10,000 mg/kg only one male and one female survived. The high dose for mice in the chronic study was therefore set at 4,000 mg/kg and the low dose at 2,000 mg/kg. No gross pathology was observed in mice at necropsy in the subchronic tests.

Design of Chronic Studies

Tables 1 and 2 show the numbers of rats and mice of each sex used in the study, including those used as matched controls. Also shown is the dosage, duration of treatment, observation period, and the time-weighted average dose for each category of test animal.

The rats were started on the study at 7 weeks of age. Those on the low dose were treated for 78 weeks, 5 days per week, with 750 mg/kg, while rats on the high dose received 1,500 mg/kg for the same period of time. Both groups were observed to 110 weeks, when the surviving animals were killed. (The high dose for rats had been set originally at 3,000 mg/kg; this dosage proved to be too toxic, however, and the study was terminated, the animals discarded, and the study restarted as indicated above (see table 1).

Table 1. Design of 1,1,1-Trichloroethane Chronic Study: Rats

Experimental Design	Initial No. of Animals	1,1,1-Trichloroethane Doses[a] (mg/kg)	Observation Period: Treated (weeks)	Observation Period: Untreated (weeks)	Time-Weighted Average Dose[b] (mg/kg)
MALE					
Control	20	0	0	110	0
Low Dose	50	750	78	32	750
High Dose	50	1,500	78	32	1,500
FEMALE					
Control	20	0	0	110	0
Low Dose	50	750	78	32	750
High Dose	50	1,500	78	32	1,500

[a]Doses (in mg/kg body weight) administered in corn oil five times per week by gavage.

[b]Time-weighted average dose = $\frac{\Sigma(\text{dose in mg/kg} \times \text{number weeks at that dose})}{\Sigma(\text{number of weeks receiving dose})}$

Table 2. Design of 1,1,1-Trichloroethane Chronic Study: Mice

Experimental Design	Initial No. of Animals	1,1,1-Trichloroethane Doses[a] (mg/kg)	Observation Period: Treated (weeks)	Observation Period: Untreated (weeks)	Time-Weighted Average Dose[b] (mg/kg)
MALE					
Control	20	0	0	90	0
Low Dose	50	2,000	10		2,807
		2,500	10		
		3,000	58		
		0		12	
High Dose	50	4,000	10		5,615
		5,000	10		
		6,000	58		
		0		12	
FEMALE					
Control	20	0	0	90	
Low Dose	50	2,000	10		2,807
		2,500	10		
		3,000	58		
		0		13	
High Dose	50	4,000	10		5,615
		5,000	10		
		6,000	58		
		0		13	

[a]Doses (in mg/kg body weight) administered in corn oil five times per week by gavage.

[b]Time-weighted average dose = $\frac{\Sigma(\text{dose in mg/kg} \times \text{number weeks at that dose})}{\Sigma(\text{number of weeks receiving dose})}$

The mice were started at 5 weeks of age and were treated 5 days per week, for a total of 78 weeks at varying dosages. Since the test chemical did not cause toxic signs, both the high and low dosages were raised twice during the treatment period. Surviving animals were observed for 12 weeks following the treatment and then killed in the 90th week of the study.

Animals which received a known carcinogen, carbon tetrachloride, served as the positive control for this study and for the entire series of halogenated chemicals tested. The purpose of this control was to verify the sensitivity of the test animals to carcinogenicity by halogenated hydrocarbons and to serve as a check on procedures and techniques. The animals used were of the same strain and source as those dosed with 1,1,1-trichloroethane. The positive control rats were housed separately from the 1,1,1-trichloroethane-dosed rats, but were in the same room as the 1,1,1-trichloroethane-dosed mice. The design of the carbon tetrachloride study (positive control) was essentially the same as that of 1,1,1-trichloroethane. The high dose for male rats was 74 mg/kg and the high dose for females 160 mg/kg. The high dose for both male and female mice was 2,500 mg/kg. Groups of males and females of both species were also administered low doses which were one-half the high doses. Untreated animals of the same strain, source, and age were used as matched controls to the carbon tetrachloride-treated (positive control) rats and mice.

Untreated animals of the same strain and source were used as untreated matched controls to the 1,1,1-trichloroethane-treated rats and mice; there were 20 animals of each sex of each species. They were started at the same time as the 1,1,1-trichloroethane-treated rats and mice and were housed in the same room as the treated animals. They received identical animal care,

except that neither the test substance nor the corn oil was administered. There were no vehicle control animals used.

Clinical and Pathologic Examinations

All animals were inspected twice daily. Body weights and food consumption were recorded weekly for the first 10 weeks and monthly thereafter. A necropsy was performed on each animal regardless of whether it died, was killed early, or survived to termination. All animals were injected with sodium pentobarbital intraperitoneally (0.3 to 0.5 ml for rats and 0.05 to 0.1 ml for mice) until they were completely anesthetized. The animals were then exsanguinated and immediately necropsied. The following tissues were taken from killed animals and, where practical, from those found dead: brain, pituitary, adrenal, thyroid, parathyroid, trachea, esophagus, thymus, salivary gland, lymph nodes (mesenteric and cervical), heart, nasal passages, lung, spleen, liver, kidney, stomach, small intestine, large intestine, pancreas, urinary bladder, prostate or uterus, seminal vesicles and testis with epididymis or ovary, skin with mammary gland, muscle, nerve, bone, bone marrow, and tissue masses.

Tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically. In evaluating suspected treatment-related effects in rats, the matched-control group was compared to the test group. Complete data on all tumors are presented for the matched controls and for the 1,1,1-trichloroethane-treated groups in Appendixes A and B. For positive (carbon tetrachloride) controls, only the data relating to survival and specific lesions of concern are presented.

The intent was to evaluate all organs, tissues, and gross lesions for every animal as specified in the pathology protocol for the Bioassay Program. However, a few tissues (especially small organs) were lost during the necropsy and the histologic preparation process; therefore, the denominator used for a particular organ, tissue, or lesion in Appendixes A and B may not necessarily equal the number of animals placed on experiment in each group.

Data Recording and Statistical Analyses

Pertinent data for this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, animal weight, and individual pathologic results as recommended by the International Union Against Cancer (UICC) (Berenblum, 1969). Data tables were generated for statistical review and verification of data transcription.

Survival probabilities were estimated by the product limit procedure of Kaplan and Meier (1958) and presented in this report in the form of graphs. Deaths due to accident are not included; all other deaths are recorded in the system. Statistical tests of differences in survival between groups are compared using the method of Cox (1972) for two groups and an extension of this method by Tarone (1975) for more than two groups.

The number of animals with tumors was analyzed as a percentage of the number of tissues examined. For some sites, such as liver or lung, the animal is counted in the denominator of the tables showing such tumors at that site only if the site had a histologic examination. For tumors that

appeared at several sites, a count is entered in the denominator for any animal that had at least one such site histologically examined for that tumor.

Statistical analysis of tumor incidence was made using the Fisher exact test (Cox 1970) to compare the controls to each dose level. In addition, the Armitage and Cochran test for linear trend in proportions with continuity correction (Armitage, 1971) was used. This test, assuming a linear trend, determines if the slope of the dose-response curve is different from zero ($P < 0.05$). The method also calculates the probability level of a departure from linear trend.

A conservative adjustment, the Bonferroni inequality (Miller, 1966) was used for simultaneous comparisons of several treatments with a control. For the comparison of k doses with a control, this correction requires a significance level less than or equal to 0.05/k for the overall comparison to be significant at the 0.05 level. This adjustment was not made in the tables where the Fisher exact test results are shown but is discussed in the analysis when appropriate.

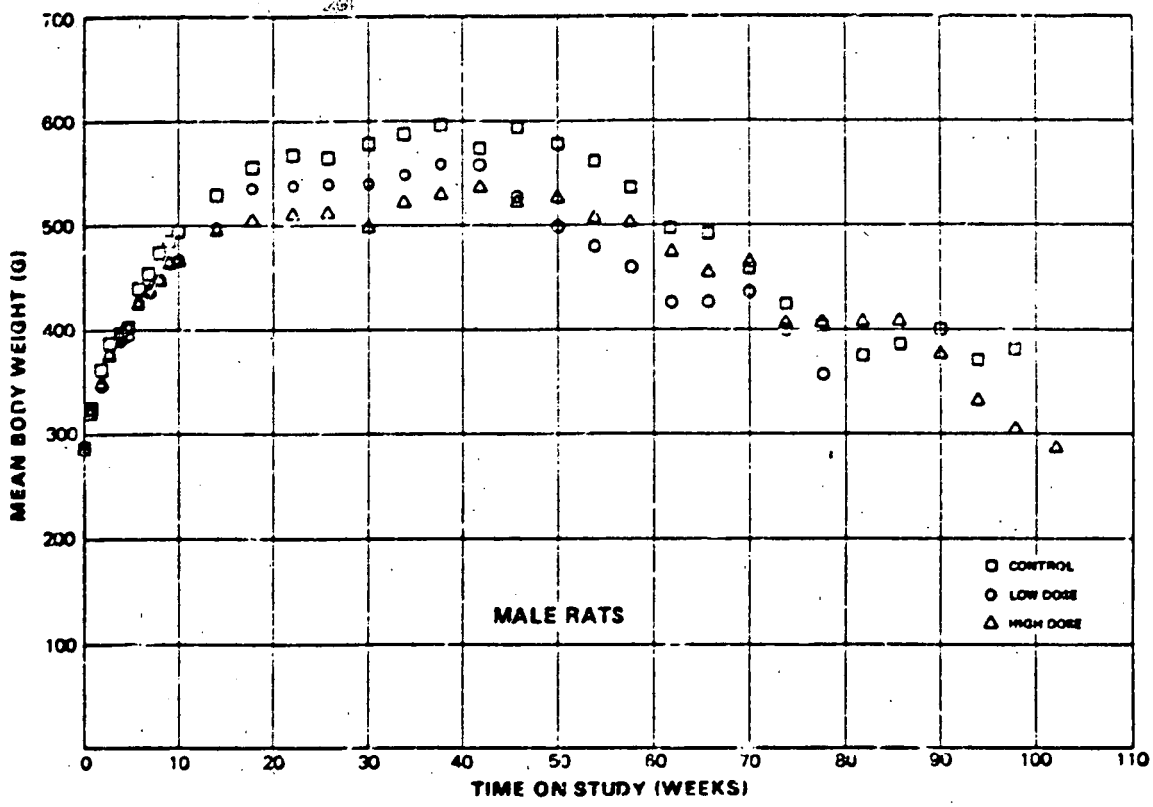
3.0 RESULTS

A. RATS

Body Weights and Clinical Signs (Rats)

Average weight gains of male rats appeared to be treatment related during the first year of the study. However, there was little difference among groups of female rats until the second year, when deaths made any comparison questionable (see figure 1).

During the first year of the study, the appearance and behavior of the treated rats were generally comparable to those of the matched controls, except that by week 10 urine stains were evident on a few animals in the treated groups. As the study progressed, increasing numbers of treated females, and, to a lesser extent, treated male rats, showed urine staining of the abdominal fur. Respiratory involvement characterized by wheezing, rapid or labored breathing, a nasal discharge that was sometimes bloody in appearance, and/or a hunched appearance were noted at a low or moderate incidence among rats in all groups, including matched controls, during the latter part of the first year. The number of treated animals showing respiratory signs increased somewhat over that of the matched controls as the study progressed. Toward the end of the experiment all surviving rats showed wheezing and a hunched appearance. Signs of aging commonly observed in laboratory rats were noted during the second year in comparable numbers of control and treated rats. These signs included rough fur, sores on the body and/or extremities, alopecia or desquamation of the tail, squinted eyes, and bloody discharge or crust around the eyes. The latter sign was noted more often in treated animals than in the matched controls.



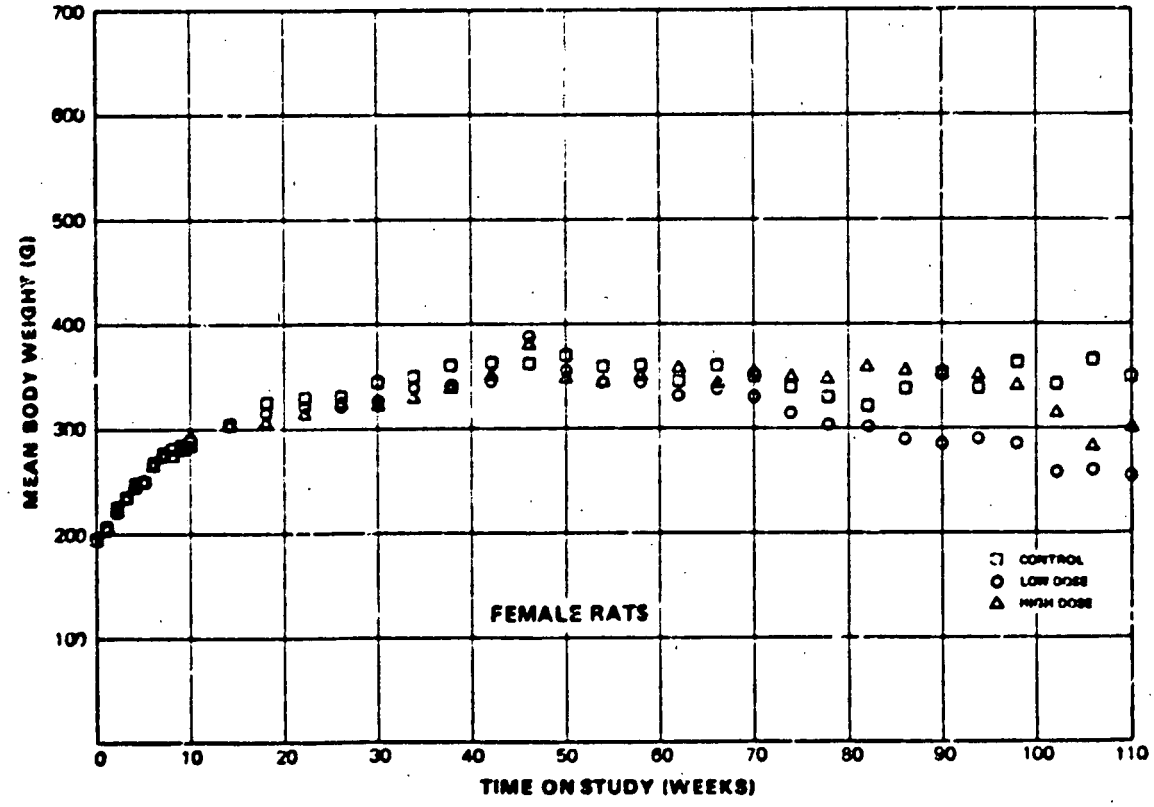


Figure 1. Growth Curves for Rats - 1,1,1-Trichloroethane

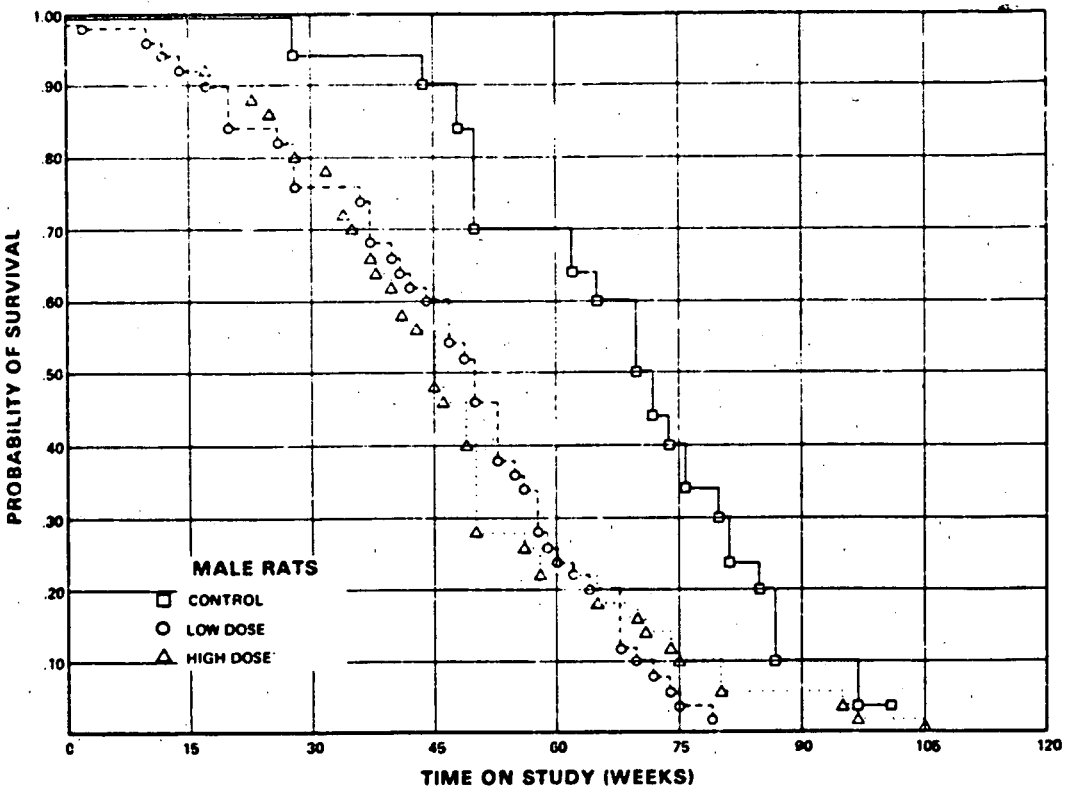
Survival (Rats)

The survival of both sexes of dosed rats was less than that of the matched-control groups. In male rats 6/20 (30%) of the controls, 32/50 (64%) of the low-dose group, and 36/50 (72%) of the high-dose group died within a year of the start of the study. The Tarone statistical test of survival showed a dose-related positive trend ($P < 0.001$) in the proportions of deaths over the period of the experiment.

In female rats 1/20 (5%) of the matched controls, 24/50 (48%) of the low-dose group, and 21/50 (42%) of the high-dose group died in the first year. As in male rats, the statistical test for positive dose-related trend was significant ($P < 0.04$). Figure 2 shows the estimated probability of survival of rats.

In both sexes, the early mortality in the 1,1,1-trichloroethane-treated rats may have affected the incidence of late-appearing tumors; this is especially true in the males, since none survived to the scheduled termination of the study.

Fewer rats receiving 1,1,1-trichloroethane survived at both 78 and 110 weeks than did the positive control rats receiving the known carcinogen, carbon tetrachloride (see table 3).



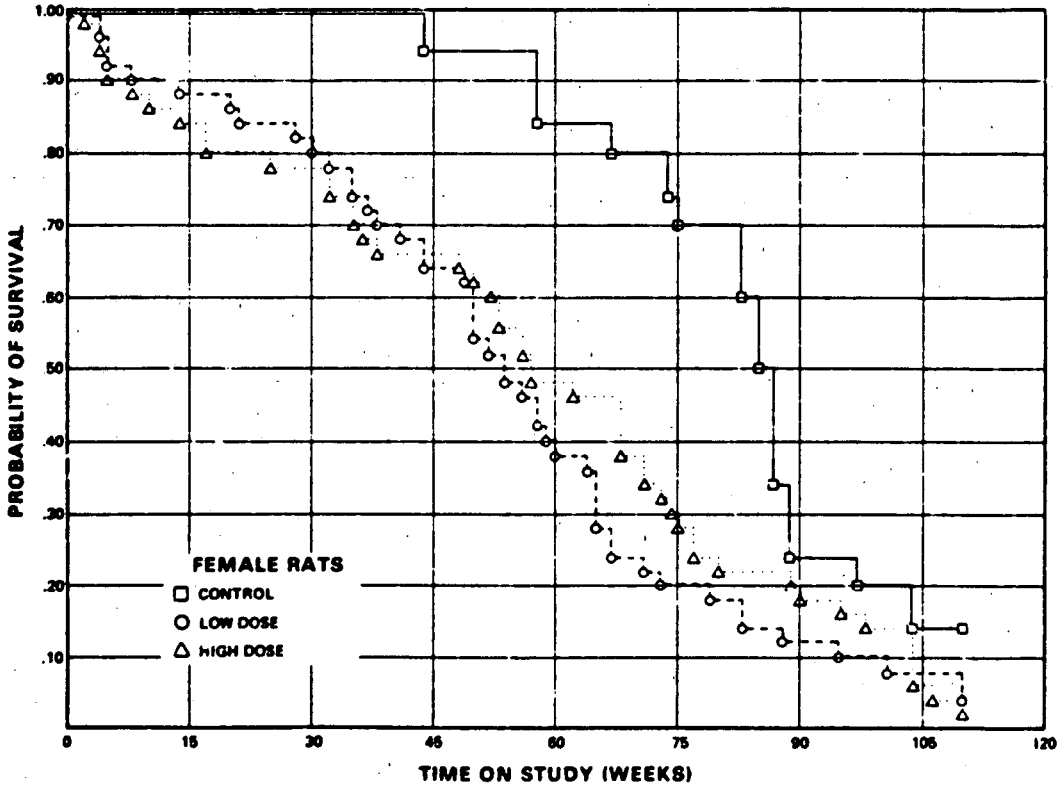


Figure 2. Survival Curves for Rats -1,1,1-Trichloroethane

Table 3. Comparison of Survival of Control Groups, 1,1,1-Trichloroethane-Treated, and Carbon Tetrachloride-Treated (Positive Control) Rats

Group	1,1,1-Trichloroethane			Carbon Tetrachloride		
	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 110 Weeks[a]	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 110 Weeks[a]
MALE						
Control	20	7	0	20	20	12
Low Dose	50	1	0	50	34	15
High Dose	50	4	0	50	35	8
FEMALE						
Control	20	14	3	20	18	14
Low Dose	50	9	2	50	38	20
High Dose	50	12	1	50	21	14

[a]Time in study at last weighing.

Pathology (Rats)

A variety of neoplasms was represented among both 1,1,1-trichloroethane-treated and matched-control animals (see Appendix A). These included hemangiosarcoma (subcutaneous tissue in the abdomen), papillary cystadenocarcinoma (mammary gland and subcutaneous tissue in the groin), lipoma (heart), hemangioma (mesenteric artery, spleen), leiomyoma (artery in thymus region), adrenal cortical adenoma, and pheochromocytoma. Some thyroid neoplasms occurred sporadically: follicular-cell adenoma and carcinoma and papillary cystadenoma. One hepatic-cell adenoma was observed. Mammary gland neoplasms included the following types: fibroadenoma, adenocarcinoma, and papillary cystadenocarcinoma. Other neoplasms were identified as follows: transitional-cell carcinoma (urinary bladder),

chromophobe adenoma, endometrial stromal polyp, malignant glioma (brains) and osteosarcoma (mesentery: metastatic).

Of the malignant neoplasms, the following occurred only in test rats: papillary cystadenocarcinoma in the subcutis of 1/50 high-dose females; urinary bladder transitional-cell carcinoma in 1/50 high-dose males; brain malignant glioma in 1/48 low-dose males, and mesenteric metastatic osteosarcoma in 1/50 high-dose females. Follicular carcinoma was observed in 1/20 matched-control females and 1/49 high-dose females. All other malignant neoplasms occurred in the matched-control animals.

Each of the types of neoplasm represented had been encountered previously as a spontaneous lesion in the rat and no relationship in type or incidence to chemical treatment was apparent.

A variety of nonneoplastic lesions was represented among both the matched-control and 1,1,1-trichloroethane-treated animals (see Appendix C). Such lesions have been encountered previously as spontaneous occurrences in aging laboratory rats.

Of the spontaneous lesions, chronic murine pneumonia was prevalent and was the most probable cause for the high incidence of natural deaths. It was characterized by a variety of inflammatory changes including abscesses, pleuritis, and bronchiectasis.

The only proliferative hepatocellular lesion (adenoma) in rats treated with 1,1,1-trichloroethane was in a high-dose female. None occurred in the

matched-control groups; however, several neoplastic nodules and hepatocellular carcinomas occurred in the positive-control rats treated with carbon tetrachloride (see table 4).

Table 4. Comparison of the Incidence of Liver Tumors in Control Groups, 1,1,1-Trichloroethane-Treated, and Carbon Tetrachloride-Treated (Positive Control) Rats

Group	Hepatocellular Carcinoma		Neoplastic Nodules	
	CCl_3CH_3	CCl_4	CCl_3CH_3	CCl_4
MALES				
Control	0/20	0/20	0/20	0/20
Low Dose	0/49	2/50	0/49	2/50
High Dose	0/50	2/50	0/50	1/50
FEMALES				
Control	0/20	0/20	0/20	0/20
Low Dose	0/50	4/49	0/50	2/49
High Dose	0/50	1/49	1/50[a]	3/49

[a]Hepatocellular adenoma.

Statistical Analyses of Results (Rats)

There were no tumors at any site that appeared in sufficient numbers to indicate a statistically significant dose relationship. Table 5 shows the incidence of those tumors that had a proportion of greater than 5% in any dose group in either sex. The proportion of the rats with tumors was higher in the untreated group of both sexes than in the dose groups. There is no statistical evidence of carcinogenicity of the chemical in these results; however, the significant difference in survival of the dosed groups compared to the controls and the low survival rate of all groups should be considered in evaluation of the data.

Table 5. Statistical Analyses of the Incidence of Tumors at Specific Sites in Matched Controls and 1,1,1-Trichloroethane-Treated Rats

Topography: Morphology	MALE			FEMALE		
	Matched Control	Low[a] Dose	High[a] Dose	Matched Control	Low[a] Dose	High[a] Dose
Total Animals: All Tumors [b]	3/20(15)	6/48(12)	6/50(13)	7/20(35)	7/50(14)	9/50(18)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	72	28	50	58	64	56
Pituitary: Chromophobe Adenoma[b]	0/20(0)	0/48(0)	0/48(0)	3/20(15)	2/48(4)	1/48(2)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	--	84	71	90
Thyroid: Follicular-Cell Adenoma or Carcinoma[b]	0/20(0)	0/48(0)	0/50(0)	2/20(10)	0/50(0)	1/49(2)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	--	103	--	97
Adrenal: Cortical Adenoma[b]	0/20	3/49(6)	1/50(2)	2/19(11)	1/48(2)	2/49(4)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor		28	106	85	99	106

[a]Low- and high-dose groups received 1,1,1-trichloroethane in corn oil by gavage five times per week in doses of 750 and 1,500 mg/kg body weight respectively.
[b]Number of tumor-bearing animals/number of animals examined at site (percent).
[c]Beneath the incidence of the matched controls is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10, otherwise N.S. - not significant. Beneath the dosed group incidence is the probability level for the Fisher exact (conditional) test for comparison of that dosed group with the matched control group when it is below 0.10, otherwise N.S. - not significant.

The first tumors observed in the male rats were hemangioma in the spleen at 72 weeks in a matched-control animal, cortical adenoma of the adrenal at 28 weeks in a low-dose animal, and lipoma in the heart at 50 weeks in a high-dose animal. In female rats, the first tumor seen was fibroadenoma in the mammary tissue at 58 weeks in a matched-control animal, endometrial stromal polyp of the uterus at 64 weeks in a low-dose animal, and papillary cystadenocarcinoma in the mammary tissue at 56 weeks in a high-dose animal.

B. MICE

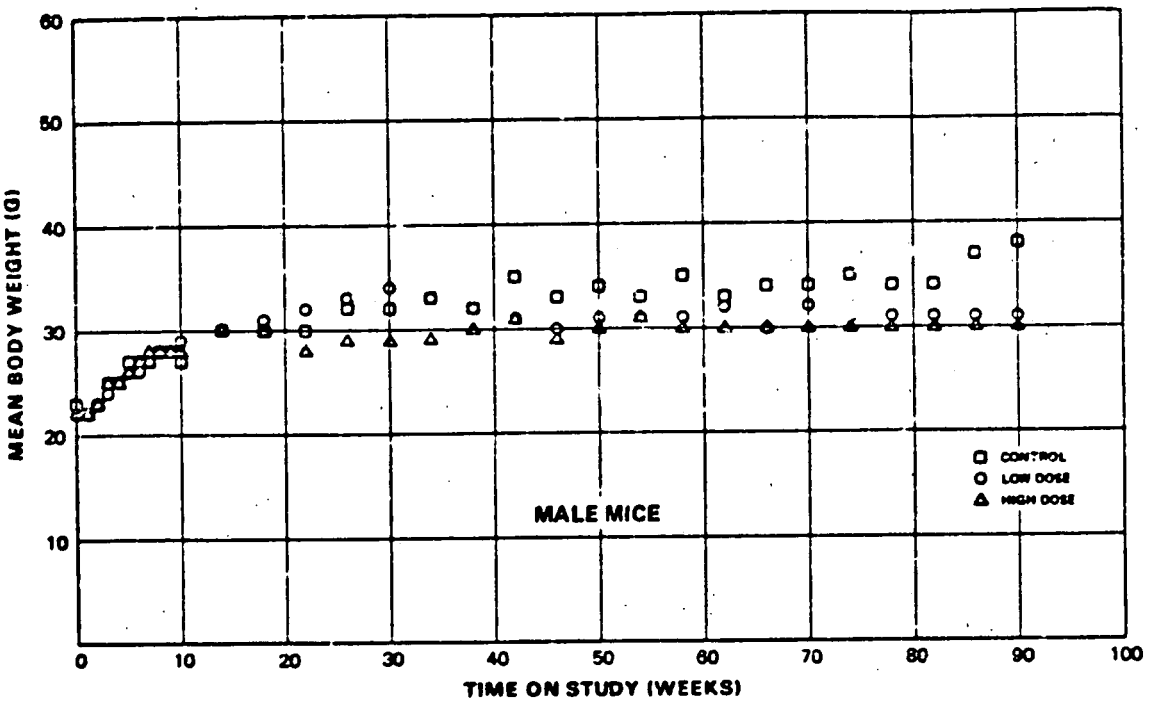
Body Weight and Clinical Signs (Mice)

Treated animals of both sexes gained less weight than did the matched controls (see figure 3). The reduction in weight gain appears directly related to the treatment.

Throughout the test, the appearance and behavior of the treated and matched-control mice were generally similar. Clinical signs commonly observed in group-housed mice and usually associated with aging were observed at a similar rate among matched-control and treated animals during the study. These signs included: alopecia (generalized or localized), sores on the back and other body parts, anal and/or penile irritation, hunched appearance, rough hair coat, and occasional abdominal distension.

Survival (Mice)

Figure 4 shows the estimated probability of survival of mice. In male mice, the Tarone test showed no significant difference between the proportions of the groups surviving (P = 0.55). In male mice, 10/20 (50%) of the matched-control group, 21/50 (42%) of the low-dose group, and 25/50



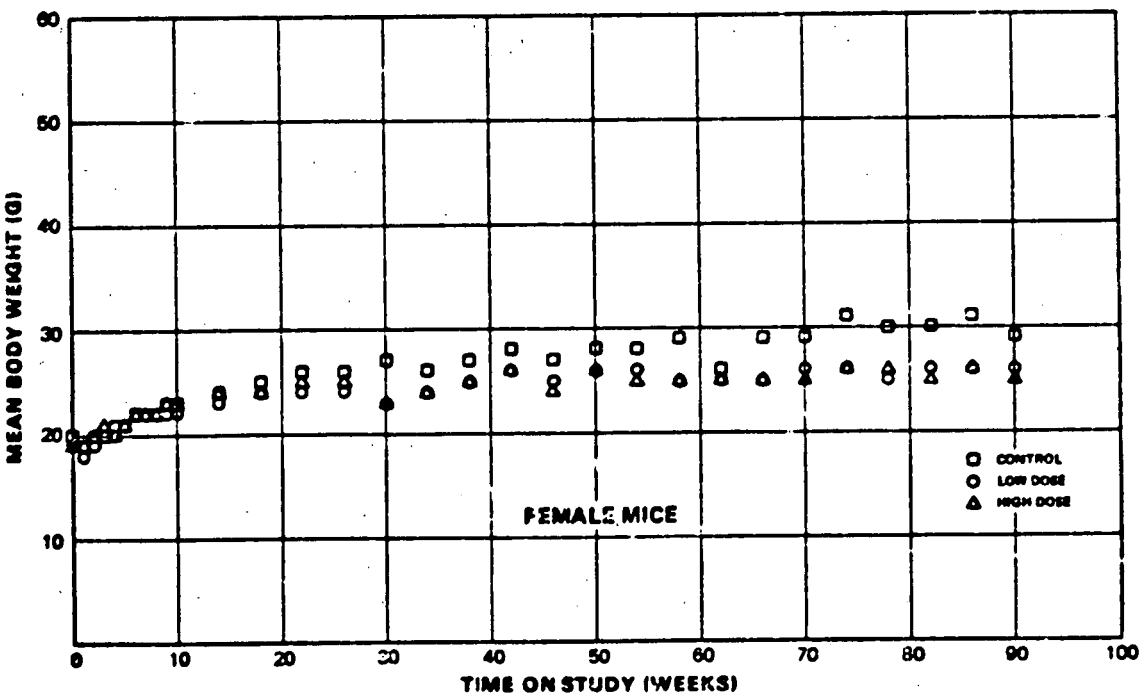
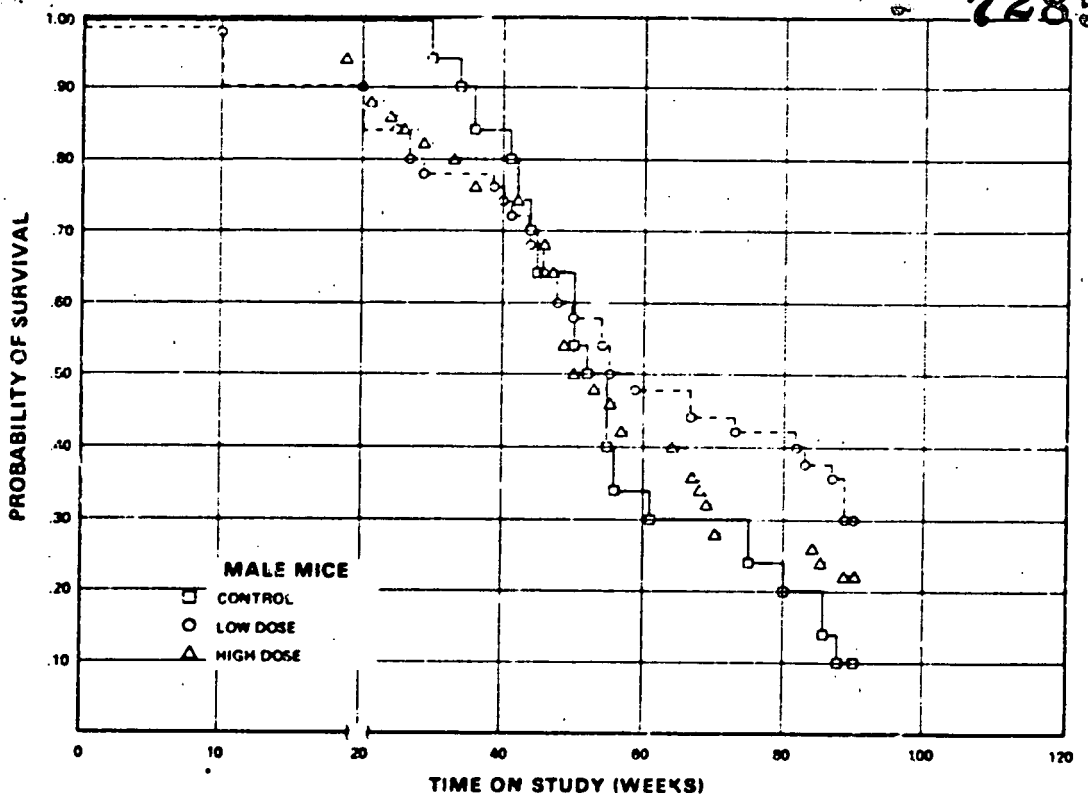


Figure 3. Growth Curves for Mice - 1,1,1-Trichloroethane



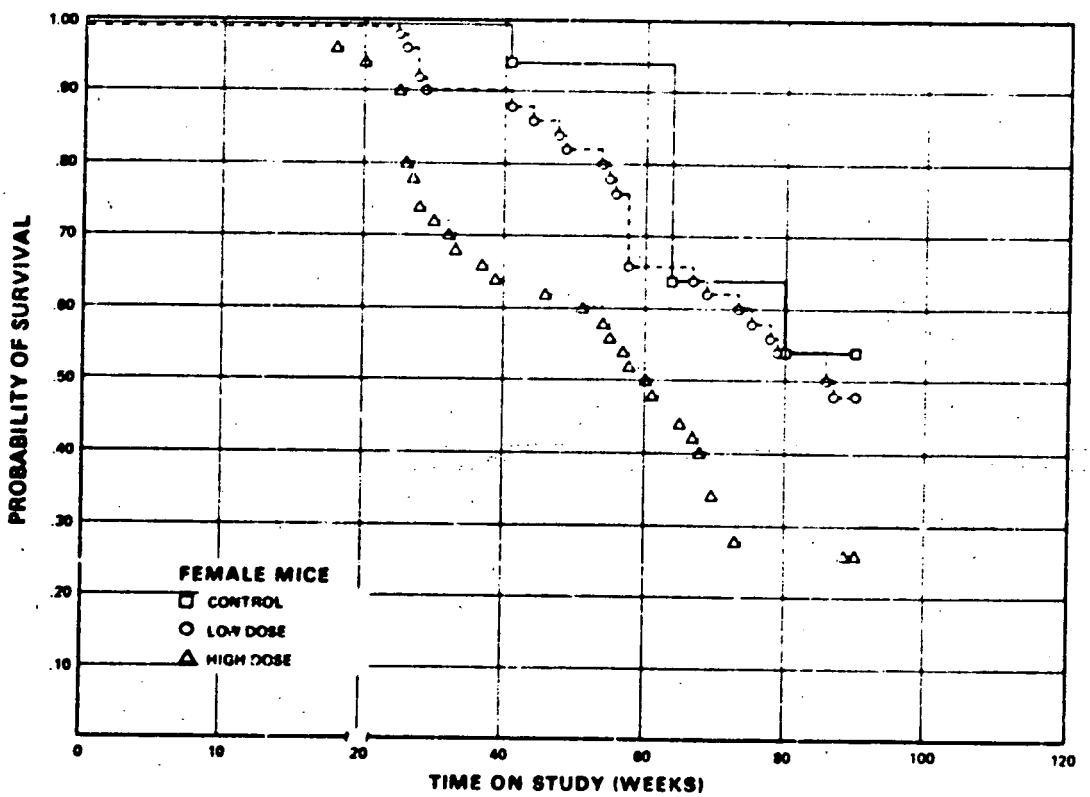


Figure 4. Survival Curves for Mice - 1,1,1-Trichloroethane

(50%) of the high-dose group died within a year of the start of the experiment.

In female mice, 1/20 (5%) of the matched-control group, 9/50 (18%) of the low-dose group, and 20/50 (40%) of the high-dose group died within the first year of the study. The Tarone test for positive dose-related trend in the proportions surviving had a significance level of P = 0.002.

Table 6 shows that while few mice receiving carbon tetrachloride survived until the planned termination of the test, from 25 to 40% of those treated with 1,1,1-trichloroethane reached the planned termination date. The high early mortality in mice receiving 1,1,1-trichloroethane may have lowered the incidence of late-appearing tumors.

Table 6. Comparison of Survival of Control Groups, 1,1,1-Trichloroethane-Treated, and Carbon Tetrachloride-Treated (Positive Control) Mice

Group	1,1,1-Trichloroethane			Carbon Tetrachloride		
	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 90 Weeks	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 90 Weeks
MALE						
Control	20	6	2	20	13	7
Low Dose	50	21	15	50	11	0
High Dose	50	14	11	50	2	1
FEMALE						
Control	20	12	11	20	18	17
Low Dose	50	28	23	50	10	0
High Dose	50	14	13	50	3	1

Pathology (Mice)

A variety of neoplasms was represented among both the 1,1,1-trichloroethane-treated and matched-control mice (see Appendix B). These included fibrosarcoma and sarcoma of the subcutis, alveolar/bronchiolar adenoma, hepatic-cell adenoma and carcinoma, cystadenocarcinoma of the ovary, and adrenal cortical adenoma. Malignant lymphoma occurred in a number of organs either at primary (lymph node, spleen) or metastatic (liver, pancreas, spleen, brain, kidney, ovary) sites.

Fibrosarcoma and sarcoma of the subcutis were observed in 1/47 low-dose females and 1/50 high-dose females, respectively. Hepatocellular carcinoma occurred in 1/49 high-dose males. Cystadenocarcinoma of the ovary occurred in 1/43 high-dose females. Malignant lymphoma of the spleen appeared in 1/15 matched-control males, 2/44 high-dose males (with liver metastases), and 1/48 low-dose females. The few other cases of malignant lymphoma occurred in matched-control animals.

Each of the types of neoplasm represented had been encountered previously as a spontaneous lesion in the mouse and no relationship in type or incidence to chemical treatment was apparent.

A variety of nonneoplastic lesions was represented among both the matched-control and chemical-treated animals (see Appendix D). Such lesions have been encountered previously as spontaneous occurrences in aging laboratory mice. Of the spontaneous lesions, chronic murine pneumonia was the most significant pathologically. It occurred in all groups of matched-control and test animals and was the probable cause for the high incidence of early death.

The nearly 100% incidence of hepatocellular carcinoma in the positive-control groups receiving carbon tetrachloride stands in marked contrast to the very low incidence among the 1,1,1-trichloroethane-treated mice and the matched-controls (see table 7).

Table 7. Comparison of the Incidence of Hepatocellular Carcinoma in Control Groups, 1,1,1-Trichloroethane-Treated, and Carbon Tetrachloride-Treated (Positive Control) Mice

Group	1,1,1-Trichloroethane	Carbon Tetrachloride
MALE		
Control	2/19	2/19
Low Dose	0/47	49/49
High Dose	1/49	47/48
FEMALE		
Control	1/20	1/20
Low Dose	0/48	40/40
High Dose	0/50	43/45

Statistical Analyses of Results (Mice)

Table 8 shows the proportions of primary tumors of the liver and malignant lymphoma that accounted for most of the tumors observed in mice. In the dosed groups the proportion of animals observed to have tumors was not statistically significant; the matched-control groups had a higher proportion of animals with tumors than any of the dosed groups. There were no vehicle controls with an environment and period of test comparable to that of the dosed groups, but, due to the low incidence of tumors in the dosed groups, the use of such vehicle-control groups could not show a

Table 8. Statistical Analyses of the Incidence of Tumors at Specific Sites in Matched Controls and 1,1,1-Trichloroethane-Treated Mice

Topography: Morphology	MALE			FEMALE		
	Matched Control	Low[a] Dose	High[a] Dose	Matched Control	Low[a] Dose	High[a] Dose
Total Animal: All Tumors[b]	2/15(13)	2/47(4)	6/49(12)	4/18(22)	2/48(5)	3/50(6)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	80	89	50	80	54	26
Hematopoietic System: Malignant Lymphoma[b]	2/15(13)	0/47(0)	2/49(4)	3/18(17)	1/48(2)	0/50(0)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S	N.S.
Weeks to First Observed Tumor	80	--	64	80	90	--
Liver: Hepatocellular Adenoma or Carcinoma, or Neoplastic Nodule[b]	0/15(0)	0/47(0)	4/49(8)	0/18(0)	0/48(0)	0/50(0)
P Values[c]	P = 0.035	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to First Observed Tumor	--	--	--	--	--	--

[a]Low- and high-dose groups received 1,1,1-trichloroethane in corn oil by gavage five times per week in time-weighted average doses of 2,807 and 5,615 mg/kg body weight, respectively.
[b]Number of tumor-bearing animals/number of animals examined at site (percent).
[c]Beneath the matched controls incidence is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10, otherwise N.S. - not significant.
Beneath the dose group incidence is the probability level for the Fisher exact test for comparison of that dosed group with the control group when it is below 0.10, otherwise N.S. - not significant.

dose-related association. The early deaths that occurred in the high-dose mice should be considered when inferences are made on the incidences of tumors observed in the groups.

The first lesions observed in the male mice were alveolar/bronchiolar tumor of the lung and malignant lymphoma in a matched-control animal at 80 weeks, hemangiosarcoma in the low-dose animal group at 89 weeks, and hepatocellular adenoma of the liver at 50 weeks in a high-dose mouse. In the females, malignant lymphoma was observed at 80 weeks in the matched group, fibrosarcoma in the subcutaneous tissue at 54 weeks in the low-dose group, and cystadenocarcinoma of the mammary at 26 weeks in the high-dose group.

The low incidence of tumors of any type precluded interpretation of age-adjusted statistical analyses.

4.0 DISCUSSION

The studies were not completely adequate tests of carcinogenicity because of the short survival time of the dosed animals.

In rats, treatment with 1,1,1-trichloroethane failed to elicit a statistically significant increase in either the total number of neoplasms or in any specific type of neoplasm. However, there was compound-related and dose-related early mortality among the rats treated with 1,1,1-trichloroethane, and insufficient numbers survived to have demonstrated a significant incidence of late-developing tumors. The observation of a small number of hepatocellular carcinomas and neoplastic nodules in the carbon tetrachloride-treated positive control rats but not in the matched controls, suggests that Osborne-Mendel rats may respond positively to a potent chlorinated hydrocarbon hepatic carcinogen, but this requires confirmation.

In the mice, as in the rats, there were no tumors that could be related to treatment. Survival of mice treated with 1,1,1-trichloroethane was longer than that of the rats. Only 3% of the rats survived to termination of the experiment, compared with 31% of the mice. However, no carcinogenic response was demonstrated.

Had the data indicated a positive carcinogenic effect for 1,1,1-trichloroethane, the presence of the inhibitor p-dioxane, or other possibly carcinogenic impurities, would have raised some questions regarding the results. However, in the present study it is evident that such carcinogenic components (Argus et al.,1965 and 1973; Hoch-Ligeti et al., 1970) of technical grade 1,1,1-trichloroethane, if present, were in such low concentrations that their influence was not revealed.

These studies cannot be regarded as appropriate tests for the carcinogenicity of 1,1,1-trichloroethane in the test animals because of the abbreviated life spans of both the rats and mice. In addition, no previous studies adequate to evaluate carcinogenicity have been reported in the literature.

5.0 BIBLIOGRAPHY

E 7285

Argus, M. F., Arcos, J.C., and Hoch-Ligeti, C. 1965. Studies on the carcinogenic activity of protein-denaturing agents: Hepatocarcinogenicity of dioxane. J. Natl. Cancer Inst. 35:949-958.

Argus, M. F., Sohal, R. S., Bryant, G. M., Hoch-Ligeti, C., and Arcos, J. C. 1973. Dose-response and ultrastructural alterations in dioxane carcinogenesis. Europ. J. Cancer 9:237-243.

Armitage, P. 1971. Statistical Methods in Medical Research, p. 135. John Wiley and Sons, New York.

Berenblum, I., ed. 1969. Carcinogenicity Testing. UICC Technical Report Series, Vol. 2. International Union Against Cancer, Geneva.

Browning, E. 1959. Toxic solvents: A review. Brit. J. Indust. Med. 16:23-39.

Chemical Economics Handbook. 1975. Chemical Information Services, Stanford Research Institute, Menlo Park, California.

Cox, D. R. 1970. Analysis of Binary Data, pp. 61-65. Methuen, London.

Cox, D. R. 1972. Regression models and life tables. J. Roy. Statist. Soc. B 34:187-220.

Della Porta, G., Terracini, B., and Shubik, P. 1961. Induction with carbon tetrachioride of liver cell carcinomas in [illegible]rs. J. Natl. Cancer Inst. 26:855-863.

Eschenbrenner, A. B. and Miller, E. 1946. Liver necrosis and the induction of carbon tetrachloride hepatomas in strain A mice. J. Natl. Cancer Inst. 6:325-341.

Hoch-Ligeti, C., Argus, M. F., and Arcos, J. C. 1970. Induction of carcinomas in the nasal cavity of rats by dioxane. Brit. J. Cancer 24:164-167.

Kaplan, E. L. and Meier, P. 1958. Nonparametric estimation from incomplete observations. J. Amer. Statist. Assn. 53:457-481.

Klassen, C. D. and Plaa, G. L. 1969. Comparison of the biochemical alterations elicited in livers from rats treated with carbon tetrachloride, chloroform, 1,1,2-trichloroethane, and 1,1,1-trichloroethane. Biochem. Pharmacol. 18:2019-2027.

Linhart, M. S., Cooper, J. A., Martin, R. L., Page, N. P., and Peters, J. A. 1974. Carcinogenesis bioassay data system. J. Comp. Biomed. Res. 7:230-248.

Miller, R. G., Jr. 1966. Simultaneous Statistical Inference. McGraw-Hill, New York.

National Cancer Institute. 1976. Carcinogenesis Bioassay of Trichloroethylene, NCI-CG-TR-2. Carcinogenesis Program, Division of Cancer Cause and Prevention, National Institutes of Health, Bethesda, Maryland. USDHEW Pub. No. (NIH) 76-802.

Reuber, M. D. and Glover, E. L. 1970. Cirrhosis and carcinoma of the liver in male rats given subcutaneous carbon tetrachloride. J. Natl. Cancer Inst. 44:419-423.

Sontag, J. M., Page, N. P., and Saffiotti, U. 1976. Guidelines for Carcinogen Bioassay in Small Rodents, NCI-CG-TR-1. Carcinogenesis Program, Division of Cancer Cause and Prevention, National Institutes of Health, Bethesda, Maryland. USDHEW Pub. No. (NIH) 76-801.

Squire, R. A. and Levitt, M. H. 1975. Report of a workshop on classification of specific hepatocellular lesions in rats. Cancer Res. 35:3214-3233.

Tarone, R. E. 1975. Tests for trend in life table analysis. Biometrika 62:679-682.

U.S. Department of Health, Education, and Welfare, Food and Drug Administration. 1973a. Trichloroethane: Aerosol Drug Products for Human Use. Federal Register 38 (No. 156): 21935-21936, 21 CFR Part 130, August 14, 1973.

U.S. Department of Health, Education, and Welfare, Food and Drug Administration, 1973b. Human drugs containing trichloroethane: Notice to drug manufacturers, Packers, and Distributors. Federal Register 38 (No. 156): 21950-21951, 21 CFR Part 130, August 14, 1973.

U.S. Department of Labor, Occupational Health and Environmental Control. 1972. Air contaminants. Federal Register 37 (No. 202): 22139-22144, 29 CFR Part 1910, October 18, 1972.

U.S. Dept. of Labor, Occupational Safety and Health Standards, Federal Register, Vol. 39, No. 125- Thursday, June 27, 1974, page 23542.

U.S. Environmental Protection Agency. 1972. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. Code of Federal Regulations, 40 CFR Sec. 180.1012.

U.S. Environmental Protection Agency, 1975. Preliminary Study of Selected Potential Environmental Contaminants - Optical Brighteners, Methyl Chloroform, Trichloroethylene, Tetrachloroethylene, Ion Exchange Resins.

Appendix A. Summary of the Incidence of Tumors in Rats Treated with 1,1,1-Trichloroethane[a]

	MALE			FEMALE		
Tissue/Response	Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
Animals at Start:	20	50	50	20	50	50
Animals Necropsied:	20	49	50	20	50	50
SKIN (Subcutaneous Tissue)						
Hemangiosarcoma	1/20 (5%)	0/45	0/50	0/18	0/47	0/50
Papillary cystadenocarcinoma	0/20	0/45	0/50	0/18	0/47	1/50 (2%)
HEART						
Lipoma	0/20	0/49	1/50 (2%)	0/20	0/49	0/49
ARTERY						
Hemangioma (Mesenteric Artery)		1/1 (100%)				
Leiomyoma (Artery in thymus region)						1/1 (100%)
LIVER						
Hepatocellular adenoma	0/20	0/49	0/50	0/20	0/50	1/50 (2%)
URINARY BLADDER						
Transitional cell carcinoma	0/20	0/47	1/50 (2%)	0/18	0/48	0/47
PITUITARY						
Chromophobe adenoma	0/20	0/47	0/47	3/20 (15%)	2/48 (4%)	1/48 (2%)

Appendix A. Summary of the Incidence of Tumors in Rats Treated with 1,1,1-Trichloroethane[a]

continued

Tissue/Response		MALE			FEMALE		
		Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
	Animals at Start:	20	50	50	20	50	50
	Animals Necropsied:	20	49	50	20	50	50
ADRENAL							
Cortical adenoma		0/20	3/49 (6%)	1/50 (2%)	2/19 (10%)	1/48 (2%)	2/49 (4%)
Pheochromocytoma		1/20 (5%)	0/49	0/50	0/19	2/48 (4%)	0/49
THYROID							
Follicular cell carcinoma		0/20	0/47	0/50	1/20 (5%)	0/50	1/49 (2%)
Follicular cell adenoma		0/20	0/47	0/50	1/20 (5%)	0/50	0/49
Papillary cystadenoma		0/20	0/47	0/50	1/20 (5%)	0/50	0/49
SPLEEN							
Hemangioma		1/20 (5%)	1/49 (2%)	0/50	0/20	0/50	0/49
MAMMARY GLAND							
Fibroadenoma		0/6	0/49	1/50 (2%)	4/18 (22%)	0/50	1/49 (2%)
Adenocarcinoma		0/6	0/49	0/50	1/18 (6%)	0/50	0/49
Papillary cystadenocarcinoma		0/6	0/49	0/50	1/18 (6%)	0/50	0/49

Appendix A. Summary of the Incidence of Tumors in Rats Exposed to Treated with 1,1,1-Trichloroethane[a]

continued

Tissue/Response		MALE			FEMALE		
		Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
	Animals at Start:	20	50	50	20	50	50
	Animals Necropsied:	20	49	50	20	50	50
UTERUS							
Endometrial stromal polyp		--	--	--	0/20	1/49 (2%)	4/49 (8%)
BRAIN							
Glioma (Malignant)		0/20	1/48 (2%)	0/50	0/20	0/49	0/49
MESENTERY							
Osteosarcoma (Metastatic)							1/1 (100%)

[a]Figures express the ratio of the number of tumors found to the number of tissues evaluated.

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Appendix B. Summary of the Incidence of Tumors in Mice Treated with 1,1,1-Trichloroethane[a]

Tissue/Response		MALE			FEMALE		
		Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
	Animals at Start:	20	50	50	20	50	50
	Animals Necropsied:	15	47	49	18	48	50
SKIN (Subcutaneous Tissue)							
Fibrosarcoma		0/15	0/46	0/47	0/18	1/47 (2%)	0/50
Sarcoma NOS		0/15	0/46	0/47	0/18	0/47	1/50 (2%)
LUNG							
Alveolar/Brochiolar adenoma		1/15 (7%)	1/47 (2%)	1/49 (2%)	0/18	0/43	1/50 (2%)
LIVER							
Hepatocellular adenoma		0/15	0/47	3/49 (6%)	0/18	0/43	0/50
Hepatocellular carcinoma		0/15	0/47	1/49 (2%)	0/18	0/48	0/50
Hemangiosarcoma		0/15	1/47 (2%)	0/49	0/18	0/48	0/50
Lymphoma (Metastatic)		1/15 (7%)	0/47	2/49 (4%)	1/18 (6%)	0/48	0/50
LYMPH NODE							
Malignant lymphoma		0/10	0/45	0/43	1/16 (6%)	0/47	0/47

Appendix B. Summary of the Incidence of Tumors in Mice Treated with 1,1,1-Trichloroethane[a]

continued

Tissue/Response		MALE			FEMALE		
		Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
	Animals at Start:	20	50	50	20	50	50
	Animals Necropsied:	15	47	49	18	48	50
PANCREAS							
Lymphoma (Metastatic)		1/13 (8%)	0/47	0/48	0/17	0/47	0/50
SPLEEN							
Malignant lymphoma		1/15 (7%)	0/46	2/44 (5%)	0/17	1/48 (2%)	0/50
Lymphoma (Metastatic)		0/15	0/46	0/44	1/17 (6%)	0/48	0/50
BRAIN							
Malignant lymphoma		0/15	0/47	0/49	1/16 (6%)	0/48	0/50
KIDNEY							
Lymphoma (Metastatic)		0/15	0/47	0/49	2/18 (11%)	0/48	0/50
OVARY							
Lymphoma (Metastatic)		--	--	--	2/15 (13%)	0/31	0/43
Cystadenocarcinoma		--	--	--	0/15	0/31	1/43 (2%)

Appendix B. Summary of the Incidence of Tumors in Mice Treated with 1,1,1-Trichloroethane[a]

continued

Tissue/Response		MALE			FEMALE		
		Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
	Animals at Start:	20	50	50	20	50	50
	Animals Necropsied:	15	47	49	18	48	50
ADRENAL							
Cortical adenoma		0/14	0/41	0/48	1/18 (6%)	0/48	0/47
MULTIPLE ORGANS							
Malignant lymphoma (Histiocytic)		1/14					
Malignant lymphoma					1/18		

[a]Figures express the ratio of the number of tumors found to the number of tissues evaluated.

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN RATS EXPOSED TO 1,1,1-TRICHLOROETHANE

TABLE C1

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY
IN MALE RATS TREATED WITH 1,1,1-TRICHLOROETHANE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20 (100%)	49 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	50
ANIMALS WITH NON-TUMOR PATHOLOGY	20 (100%)	48 (98%)	50 (100%)
INTEGUMENTARY SYSTEM *	2 (10%)		
SKIN	2		
EDEMA	2		
SUBCUTISSUE	2		
EDEMA	2		
RESPIRATORY SYSTEM	20 (100%)	48 (98%)	50 (100%)
TRACHEA	10	23	23
INFLAMMATION			1
ULCER		5	1
INFLAMMATION SUPPURATIVE		1	2
INFLAMMATION ACUTE	2	6	7
ULCER ACUTE		7	11
INFLAMMATION ACUTE SUPPURATIVE			1
INFLAMMATION SUBACUTE	8	8	1
TRACHEAL SUBMUCOSA		8	2
HEMORRHAGE		8	2
LUNG/BRONCHUS	10	15	28
BRONCHIECTASIS	10	10	6
ULCER		1	
INFLAMMATION ACUTE		1	7
ULCER ACUTE			6
INFLAMMATION ACUTE SUPPURATIVE		2	5
INFLAMMATION CHRONIC		1	
INFLAMMATION CHRONIC SUPPURATIVE			1
LUNG/BRONCHIOLE		10	6
INFLAMMATION ACUTE SUPPURATIVE		2	1
INFLAMMATION SUBACUTE		3	1
INFLAMMATION CHRONIC		9	
INFLAMMATION CHRONIC SUPPURATIVE			3
FIBROSIS			1

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TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
LUNG	20	28	29
BRONCHIECTASIS			1
CONGESTION		8	6
EDEMA		2	1
INFLAMMATION FOCAL			1
BRONCHOPNEUMONIA ACUTE	1		6
INFLAMMATION ACUTE		2	5
INFLAMMATION ACUTE SUPPURATIVE	9	7	8
BRONCHOPNEUMONIA ACUTE SUPPURATI			2
ABSCESS			
PNEUMONIA CHRONIC BOVINE			
INFLAMMATION CHRONIC	5		
INFLAMMATION FOCAL CHRONIC	4		
INFLAMMATION CHRONIC SUPPURATIVE	7	11	2
BRONCHOPNEUMONIA CHRONIC SUPPURA		1	2
ABSCESS CHRONIC		1	1
INFLAMMATION GRANULOMATOUS			1
FIBROSIS DIFFUSE		1	
LUNG/ALVEOLI	1	19	25
COLLAPSE	1	2	
EDEMA		17	25
CIRCULATORY SYSTEM	2 (10%)	5 (10%)	7 (14%)
ATRIUM		1	
THROMBOSIS		1	
MYOCARDIUM			1
INFLAMMATION CHRONIC			1
FIBROSIS			
DEGENERATION			
PERICARDIUM			
INFLAMMATION			
EPICARDIUM	1	8	6
INFLAMMATION		1	
INFLAMMATION ACUTE	1		
INFLAMMATION ACUTE FIBRINOUS		1	
INFLAMMATION SUBACUTE		1	4
INFLAMMATION CHRONIC		1	2
LIPO-GRANULOMA			1
NECROSIS FAT			1
AORTA			
MEDIAL CALCIFICATION			

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
CORONARY ARTERY			
MEDIAL CALCIFICATION			
MESENTERIC ARTERY			
MEDIAL CALCIFICATION			
PORTAL VEIN	1		
THROMBOSIS	1		
DIGESTIVE SYSTEM	17 (85%)	8 (16%)	7 (14%)
SALIVARY GLAND		1	
INFLAMMATION ACUTE		1	
LIVER	13	4	3
CONGESTION	11	1	3
ABSCESS CHRONIC		1	
PELIOSIS HEPATIS			
NECROSIS FOCAL	1	2	
INFARCT	1		
METAMORPHOSIS FATTY			
HYPERTROPHY	1		
LIVER/CENTRILOBULAR	1		
CONGESTION	1		
LIVER/PERIPORTAL	1		
FIBROSIS	1		
LIVER/KUPFFER CELL			1
HYPERTROPHY			1
BILE DUCT	1		
HYPERPLASIA	1		
PANCREAS	3		
INFLAMMATION CHRONIC	2		
PERIARTERITIS	1		
ESOPHAGUS		2	
DILATION		1	
FOREIGN-BODY GRANULOMA		1	
STOMACH	2		
HEMORRHAGE	1		

TABLE C1 MALE RATS: NONTUMOR PATHOLOG (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
STOMACH (CONT.)			
ULCER	1		
INFLAMMATION FOCAL			
CALCIUM DEPOSITION			
GASTRIC MUCOSA		2	2
HEMORRHAGE		2	2
SMALL INTESTINE	1		
HEMORRHAGE	1		
LARGE INTESTINE			1
INFLAMMATION ACUTE HEMORRHAGIC			1
COLONIC SUBMUCOSA	1		
HEMORRHAGE	1		
URINARY SYSTEM	16 (80%)	18 (37%)	22 (44%)
KIDNEY	10	13	20
MINERALIZATION		1	
HYDRONEPHROSIS		3	1
CONGESTION	4	3	7
HEMORRHAGE		1	
PYELONEPHRITIS			
ABSCESS			1
INFLAMMATION CHRONIC	5	6	11
INFLAMMATION CHRONIC CYSTIC	1		
INFARCT HEALED			2
KIDNEY/CORTEX	1	4	
HEMORRHAGE		1	
ABSCESS		3	
FIBROSIS DIFFUSE	1		
RENAL TUBULE	8	1	5
DILATATION	8	1	5
CAST	3	1	5
URINARY BLADDER	2	1	
HEMORRHAGE	1		

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY BLADDER (CONT.)			
ULCER ACUTE		1	
ULCER CHRONIC	1		
ENDOCRINE SYSTEM	4 (20%)	10 (20%)	8 (16%)
PITUITARY		3	3
CYST		3	3
ADRENAL	2	2	1
CYST			
CONGESTION			1
HEMORRHAGE	1		
HEMATOCYST			1
ANGIECTASIS	1	1	
METAPLASIA OSSEOUS		1	
ADRENAL CORTEX	3	5	3
HEMORRHAGE	1		
DEGENERATION			
LIPOIDOSIS	2	5	3
ADRENAL MEDULLA		1	
CYST			
HYPERPLASIA		1	
THYROID	1	1	1
CYST	1	1	1
PARATHYROID			2
HYPERPLASIA			2
PANCREATIC ISLETS			1
HYPERPLASIA			1
HEMATOPOIETIC SYSTEM	13 (65%)	27 (55%)	19 (38%)
BONE MARROW	2	3	
HYPERPLASIA HEMATOPOIETIC	2	3	

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
SPLEEN	12	19	16
CONGESTION		3	
INFLAMMATION ACUTE	1		
HEMOSIDEROSIS	10	11	9
ATROPHY		1	
LYMPHOID DEPLETION		1	
MYELOID METAPLASIA	1	6	7
HEMATOPOIESIS			
LYMPH NODE	6	14	10
LYMPHANGIECTASIS	1	2	
CONGESTION	3	6	2
EDEMA		1	
HEMORRHAGE			1
INFLAMMATION	1		
INFLAMMATION ACUTE		3	
INFLAMMATION ACUTE HEMORRHAGIC			2
INFLAMMATION SUBACUTE	1		
HYPERPLASIA RETICULUM-CELL		3	5
LYMPHOID HYPERPLASIA		1	
THYMUS		3	
CONGESTION		1	
HEMORRHAGE		2	
REPRODUCTIVE SYSTEM	7 (35%)	14 (29%)	12 (24%)
MAMMARY GLAND		1	
CYST		1	
PROSTATE	3	8	9
EDEMA		1	
INFLAMMATION			
INFLAMMATION ACUTE	1	3	3
INFLAMMATION ACUTE SUPPURATIVE	1		
INFLAMMATION SUBACUTE		1	
INFLAMMATION CHRONIC		3	2
INFLAMMATION CHRONIC SUPPURATIVE	1		2
FIBROSIS DIFFUSE			2
ATROPHY	1		1
SEMINAL VESICLE		1	1
INFLAMMATION ACUTE		1	1
TESTIS	6	8	4
ATROPHY	2	2	2
ATROPHY FOCAL		2	
ASPERMATOGENESIS	4	4	2

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
EPIDIDYMIS	1		
NECROSIS FAT			
ATROPHY	1		
NERVOUS SYSTEM	1 (5%)	1 (2%)	
BRAIN/MENINGES	1	1	
INFLAMMATION ACUTE		1	
INFLAMMATION GRANULOMATOUS	1		
BRAIN	1		
ABSCESS	1		
MUSCULOSKELETAL SYSTEM			
BONE			
SPECIAL SENSE ORGANS			
EYE			
ALL OTHER SYSTEMS		1 (2%)	2 (4%)
ADRENAL			1
LIPO-GRANULOMA			1
NECROSIS FAT			1
PLEURA		1	1
INFLAMMATION ACUTE		1	
INFLAMMATION SUBACUTE			1
NO LESION REPORTED			
AUTOLYSIS/NO NECROPSY PERFORMED		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH*	20	50	49
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE			

* INCLUDES AUTOLYZED ANIMALS

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

TABLE C2

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN FEMALE RATS TREATED WITH 1,1,1-TRICHLOROETHANE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20 (100%)	50 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
ANIMALS WITH NON-TUMOR PATHOLOGY	20 (100%)	49 (98%)	50 (100%)
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM *	20 (100%)	47 (94%)	49 (98%)
TRACHEA	9	14	17
ULCER			1
INFLAMMATION SUPPURATIVE			2
INFLAMMATION ACUTE	3	9	4
ULCER ACUTE	1	3	7
INFLAMMATION SUBACUTE	5	2	3
LUNG/BRONCHUS	15	15	14
BRONCHIECTASIS	15	7	8
INFLAMMATION ACUTE		1	3
ULCER ACUTE		2	
INFLAMMATION ACUTE SUPPURATIVE		3	1
INFLAMMATION CHRONIC	2		
ULCER CHRONIC	1		
INFLAMMATION CHRONIC SUPPURATIVE		2	2
LYMPHOID HYPERPLASIA		1	
LUNG/BRONCHIOLE	3	2	3
INFLAMMATION CHRONIC	2		
INFLAMMATION CHRONIC SUPPURATIVE		1	3
FIBROSIS	1	1	
LUNG	19	36	37
CONGESTION		7	21
EDEMA		3	4
HEMORRHAGE			1
BRONCHOPNEUMONIA			1
INFLAMMATION	1		
BRONCHOPNEUMONIA ACUTE		6	5
INFLAMMATION ACUTE	2		
INFLAMMATION ACUTE SUPPURATIVE	2	9	5
BRONCHOPNEUMONIA ACUTE SUPPURATI		8	2

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
LUNG (CONT.)			
PNEUMONIA CHRONIC NURIVE			
INFLAMMATION CHRONIC		1	
BRONCHOPNEUMONIA CHRONIC		1	
INFLAMMATION FOCAL CHRONIC	2		
INFLAMMATION CHRONIC SUPPURATIVE	12	5	7
BRONCHOPNEUMONIA CHRONIC SUPPURA	1	4	8
ABSCESS CHRONIC		3	
FIBROSIS DIFFUSE	3	2	1
LUNG/ALVEOLI	3	10	18
COLLAPSE	3	1	2
EDEMA		9	16
CIRCULATORY SYSTEM	2 (10%)	17 (34%)	20 (40%)
HEART	1		1
ABSCESS CHRONIC			1
FIBROSIS DIFFUSE	1		
MYOCARDIUM			1
INFLAMMATION SUBACUTE			1
PERICARDIUM			
INFLAMMATION			
EPICARDIUM	1	17	18
INFLAMMATION		1	
INFLAMMATION ACUTE		2	1
INFLAMMATION ACUTE FIBRINOUS		1	
INFLAMMATION SUBACUTE		4	7
INFLAMMATION CHRONIC	1	8	3
INFLAMMATION CHRONIC SUPPURATIVE			1
FIBROSIS		1	5
DIGESTIVE SYSTEM	12 (60%)	9 (18%)	16 (32%)
SALIVARY GLAND			1
CYST			
ABSCESS CHRONIC			1
LIVER	6	2	8
CONGESTION	5	1	3
NECROSIS	1		
METAMORPHOSIS FATTY			
ATROPHY	1	1	
ANGIECTASIS			1
HEPATIC CAPSULE		1	
FIBROSIS		1	

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
LIVER/CENTRILOBULAR		1	2
NECROSIS		1	
ATROPHY			2
LIVER/PERIPORTAL	1		2
FIBROSIS	1		2
BILE DUCT		2	3
INFLAMMATION CHRONIC	1		
HYPERPLASIA	2	2	3
PANCREAS	1		1
INFLAMMATION CHRONIC	1		
PERIARTERITIS			1
PANCREATIC ACINUS	1		
ATROPHY	1		
ESOPHAGUS			2
GRANULOMA			1
FIBROSIS			1
STOMACH	2	2	1
INFLAMMATION HEMORRHAGIC	1		
INFLAMMATION ACUTE		1	
ULCER ACUTE	1		
INFLAMMATION SUBACUTE			1
INFLAMMATION CHRONIC		1	
GASTRIC MUCOSA		2	2
EDEMA			1
HEMORRHAGE		2	1
SMALL INTESTINE	1		
ULCER CHRONIC	1		
LARGE INTESTINE			1
EDEMA			1
COLON			1
INFLAMMATION ACUTE			1

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
CRIMARY SYSTEM	15 (75%)	23 (96%)	15 (30%)
KIDNEY	12	21	13
MINERALIZATION	2	5	2
HYDRONEPHROSIS	1		2
CONGESTION	7	14	7
HEMORRHAGE			1
PYELONEPHRITIS			
ABSCESS		1	
INFLAMMATION CHRONIC	4	2	1
CALCIUM DEPOSITION			
KIDNEY/CORTEX			1
FIBROSIS			1
RENAL TUBULE	4	3	2
DILATATION	4	3	2
CAST	4	3	2
ENDOCRINE SYSTEM	12 (60%)	19 (38%)	21 (42%)
PITUITARY	2	4	6
CYST	2	4	6
ADRENAL	9	16	15
CONGESTION	7	14	13
EDEMA		1	
HEMORRHAGE		2	3
HEMATOCYST		1	
ANGIECTASIS	3		8
ADRENAL CORTEX	3	8	10
CYST		1	
DEGENERATION			
LIPOIDOSIS	3	8	10
HYPERTROPHY			1
ANGIECTASIS			
ADRENAL MEDULLA	1		2
HYPERPLASIA	1		2
THYROID	2		
DILATATION	1		
FOLLICULAR CYST			
HYPERPLASIA C-CELL	1		
PARATHYROID	1		
CONGESTION	1		

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
PANCREATIC ISLETS	1		
HYPERPLASIA	1		
HEMATOPOIETIC SYSTEM	18 (90%)	34 (68%)	34 (68%)
BONE MARROW		1	4
CONGESTION			1
HEMORRHAGE			1
HYPERPLASIA HEMATOPOIETIC		1	3
SPLEEN	17	26	29
CONGESTION	1	4	1
INFLAMMATION ACUTE		2	1
HEMOSIDEROSIS	10	9	9
HYPERPLASIA RETICULUM-CELL	1		
MYELOID METAPLASIA	10	11	19
LYMPH NODE	6	10	16
LYMPHANGIECTASIS		3	2
CONGESTION	3	5	3
HEMORRHAGE		2	2
INFLAMMATION	1		
INFLAMMATION ACUTE		3	1
INFLAMMATION SUBACUTE	3		
INFLAMMATION CHRONIC GRANULOMA		1	1
HEMOSIDEROSIS	2		
PLASMACYTOSIS		1	1
HYPERPLASIA RETICULUM-CELL	2	1	5
LYMPHOID HYPERPLASIA		6	4
MYELOID METAPLASIA			1
REPRODUCTIVE SYSTEM	4 (20%)	8 (16%)	5 (10%)
VAGINA			
INFLAMMATORY POLYP			
UTERUS		3	4
HYDROMETRA		2	2

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
UTERUS (CONT.)			
HEMORRHAGE		1	
INFLAMMATION ACUTE SUPPURATIVE			1
INFLAMMATION CHRONIC SUPPURATIVE			1
UTERUS/ENDOMETRIUM	4	6	4
CYST		1	2
INFLAMMATION ACUTE	3	3	1
INFLAMMATION ACUTE CYSTIC	1	1	1
HYPERPLASIA		1	
OVARY			
CYST			
NERVOUS SYSTEM	2 (10%)	2 (4%)	1 (2%)
CHOROID PLEXUS	1		
ANGIECTASIS	1		
BRAIN	1	1	1
ABSCESS		1	
GLIOSIS	1		
ATROPHY			1
MEDULLA OBLONGATA		1	
ABSCESS		1	
MUSCULOSKELETAL SYSTEM		1 (2%)	
SKELETAL MUSCLE		1	
INFLAMMATION ACUTE		1	
SPECIAL SENSE ORGANS			
BONE			

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS	1 (5%)	4 (8%)	9 (18%)
ABDOMEN		1	
LIPO-GRANULOMA		1	
NECROSIS FAT		1	
MEDIASTINUM			4
INFLAMMATION ACUTE SUPPURATIVE			1
ABSCESS CHRONIC			2
FIBROSIS			1
PLEURA	1	3	7
INFLAMMATION			
INFLAMMATION ACUTE SUPPURATIVE		1	
INFLAMMATION SUBACUTE			1
INFLAMMATION CHRONIC	1	2	6
NO LESION REPORTED		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH*	16	48	47
MORIBUND SACRIFICE	1		2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	3	2	1

* INCLUDES AUTOLYZED ANIMALS

• SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN MICE EXPOSED TO 1,1,1-TRICHLOROETHANE

TABLE C1

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY
IN MALE MICE TREATED WITH 1,1,1-TRICHLOROETHANE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	19 (100%)	47 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	15	47	49
ANIMALS WITH NON-TUMOR PATHOLOGY	14 (93%)	45 (96%)	49 (98%)
INTEGUMENTARY SYSTEM *	2 (13%)	12 (26%)	15 (30%)
SKIN	1	12	15
EDEMA			1
ULCER			1
INFLAMMATION ACUTE		1	
ABSCESS CHRONIC	1		
ACANTHOSIS		11	14
PARAKERATOSIS		2	
SUBCUT TISSUE	1		
EDEMA	1		
ABSCESS			
RESPIRATORY SYSTEM	10 (67%)	40 (85%)	46 (92%)
TRACHEA		2	
INFLAMMATION		2	
LUNG	10	40	46
CONGESTION	9	18	31
EDEMA		11	18
HEMORRHAGE		1	
BRONCHOPNEUMONIA		1	3
INFLAMMATION	1	9	9
BRONCHOPNEUMONIA ACUTE		8	1
ABSCESS		1	1
PNEUMONIA CHRONIC MURINE			
BRONCHOPNEUMONIA CHRONIC		3	
CIRCULATORY SYSTEM	1 (7%)		
AORTA	1		
INFLAMMATION ACUTE	1		

TABLE D1 MALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM	8 (53%)	13 (28%)	5 (10%)
LIVER	8	9	5
HEMATOMA		1	
LYMPHOCYTIC INFLAM INFILTRATE			2
AMYLOIDOSIS	7	4	1
HYPERPLASIA		4	2
ANGIECTASIS	1		
LIVER/CENTRILOBULAR		2	
NECROSIS FOCAL		1	
LIVER/KUPFFER CELL		1	
HYPERPLASIA		1	
PANCREAS		1	
PERIARTERITIS		1	
SMALL INTESTINE		1	
LYMPHOID HYPERPLASIA		1	
COLON			
HEMATODIASIS			
URINARY SYSTEM	13 (87%)	7 (15%)	7 (14%)
KIDNEY	12	5	7
HYDRONEPHROSIS			6
LYMPHOCYTIC INFLAM INFILTRATE	2		1
INFLAMMATION ACUTE SUPPURATIVE	2		
INFLAMMATION CHRONIC	4	4	
INFLAMMATION CHRONIC CYSTIC		1	
FIBROSIS DIFFUSE	2		
AMYLOIDOSIS	3	1	
KIDNEY/CORTEX		2	
LYMPHOCYTIC INFLAM INFILTRATE		2	
RENAL TUBULE	2		
CYTOPLASMIC VACUOLIZATION	2		
URINARY BLADDER			
INFLAMMATION			

TABLE D1 MALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM	3 (20%)		
ADRENAL	3		
AMYLOIDOSIS	3		
HEMATOPOIETIC SYSTEM	10 (67%)	15 (32%)	14 (28%)
BONE MARROW	1		1
HYPERPLASIA HEMATOPOIETIC	1		1
SPLEEN	8	9	7
AMYLOIDOSIS	7	4	
HYPERPLASIA HEMATOPOIETIC		1	
LYMPHOID HYPERPLASIA	1	3	3
MYELOID METAPLASIA		2	4
LYMPH NODE	3	9	9
CONGESTION	2	3	4
HEMORRHAGE		1	
INFLAMMATION ACUTE		1	
LYMPHOID DEPLETION	1		
HYPERPLASIA RETICULUM-CELL		5	
LYMPHOID HYPERPLASIA	1	1	5
CERVICAL LYMPH NODE			
ANGIECTASIS			
SUPERIOR DEEP CERVIC			
ANGIECTASIS			
REPRODUCTIVE SYSTEM	1 (7%)		1 (2%)
PROSTATE	1		
INFLAMMATION ACUTE	1		
SEMINAL VESICLE			1
DILATATION			1
EPIDIDYMIS			
SPERMATOGENIC GRANULOMA			

TABLE D1 MALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM	1 (7%)		
BRAIN/MENINGES	1		
INFLAMMATION ACUTE	1		
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS			
NONE			
NO LESION REPORTED	1	2	
AUTOLYSIS/NECROPSY PERF/NO HISTO			1
AUTOLYSIS/NO NECROPSY PERFORMED	4	3	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH*	17	35	37
MORIBUND SACRIFICE			2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	2	15	11
MISSING	1		

* INCLUDES AUTOLYZED ANIMALS

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

TABLE D2

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY
IN FEMALE MICE TREATED WITH 1,1,1-TRICHLOROETHANE

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	18 (100%)	48 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	18	48	50
ANIMALS WITH NON-TUMOR PATHOLOGY	18 (100%)	48 (100%)	50 (100%)
RESPIRATORY SYSTEM *	14 (78%)	42 (88%)	43 (86%)
TRACHEA			1
INFLAMMATION ACUTE			1
LUNG/BRONCHUS			1
INFLAMMATORY POLYP			1
LUNG	14	42	43
CONGESTION	9	16	29
EDEMA	1	6	13
HEMORRHAGE		6	2
INFLAMMATION	4	24	17
INFLAMMATION ACUTE SUPPURATIVE		6	3
BRONCHOPNEUMONIA ACUTE SUPPURATI		1	2
PNEUMONIA CHRONIC MURINE			
BRONCHOPNEUMONIA CHRONIC	1		
CIRCULATORY SYSTEM		1 (2%)	
MYOCARDIUM		1	
INFLAMMATION ACUTE		1	
DIGESTIVE SYSTEM	4 (22%)	14 (29%)	8 (16%)
SALIVARY GLAND		1	
LYMPHOCYTIC INFLAM INFILTRATE		1	

TABLE D2 FEMALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
LIVER	3	13	8
LYMPHOCYTIC INFLAM INFILTRATE	2	1	
INFLAMMATION SUBACUTE	1		
NECROSIS			6
NECROSIS FOCAL			1
AMYLOIDOSIS		7	1
HYPERPLASIA		2	
ANGIECTASIS		1	
LYMPHOID HYPERPLASIA		1	
MYELOID METAPLASIA		1	
LIVER/CENTRILOBULAR		1	
NECROSIS		1	
PANCREATIC DUCT			
DILATATION			
STOMACH	1		
ULCER ACUTE	1		
SMALL INTESTINE	1		
LYMPHOID HYPERPLASIA	1		
COLON			
NEMATODIASIS			
URINARY SYSTEM	6 (33%)	9 (19%)	2 (4%)
KIDNEY	5	9	2
HYDRONEPHROSIS	1	4	2
PYELONEPHRITIS			
LYMPHOCYTIC INFLAM INFILTRATE	4	1	
INFLAMMATION ACUTE SUPPURATIVE		2	
INFLAMMATION CHRONIC	1	3	
INFLAMMATION CHRONIC CYSTIC		2	
ATROPHY			
URINARY BLADDER	1		
LYMPHOCYTIC INFLAM INFILTRATE	1		

TABLE D2 FEMALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM	1 (6%)	6 (13%)	1 (2%)
ADRENAL		5	1
CONGESTION		1	1
AMYLOIDOSIS		4	
ADRENAL CORTEX	1	1	
HYPERPLASIA	1	1	
HEMATOPOIETIC SYSTEM	8 (44%)	26 (54%)	11 (22%)
BONE MARROW	3	4	
HEMORRHAGE	1		
HYPERPLASIA HEMATOPOIETIC	2	4	
SPLEEN	6	24	11
CONGESTION		1	
INFLAMMATION ACUTE	1	3	
AMYLOIDOSIS		7	1
ATROPHY		1	1
HYPERPLASIA FOLLICULAR-CELL			1
HYPERPLASIA HEMATOPOIETIC			1
LYMPHOID HYPERPLASIA	5	4	4
MYELOID METAPLASIA		10	6
LYMPH NODE	3	8	1
HEMORRHAGE		1	
INFLAMMATION ACUTE		1	
INFLAMMATION ACUTE SUPPURATIVE		1	
INFLAMMATION CHRONIC	1		
PLASMA CELL INFILTRATE		1	
HYPERPLASIA RETICULUM-CELL		1	
LYMPHOID HYPERPLASIA	2	3	1
REPRODUCTIVE SYSTEM	15 (83%)	27 (56%)	23 (46%)
VAGINA		1	
INFLAMMATION CHRONIC		1	
UTERUS	1	2	3
HYDROMETRA		2	3
INFLAMMATION			
INFLAMMATION ACUTE SUPPURATIVE	1		
UTERUS/ENDOMETRIUM	15	26	19
CYST			7

TABLE D2 FEMALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
UTERUS/ENDOMETRIUM (CONT.)			
HYPERPLASIA		1	
HYPERPLASIA CYSTIC	15	25	12
FALLOPIAN TUBE			1
DILATATION			1
OVARY	5	4	2
CYST	2	2	1
FOLLICULAR CYST	1	2	
HEMORRHAGE			1
ATROPHY	2		
ANGIECTASIS		1	
NERVOUS SYSTEM			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS		2 (4%)	
PLEURA		2	
INFLAMMATION ACUTE		2	
NO LESION REPORTED			
AUTOLYSIS/NO NECROPSY PERFORMED	2	2	
ANIMAL DISPOSITION SUMMARY			
ANIMALS LEFT IN STUDY	20	50	50
NATURAL DEATH*	9	27	36
MORIBUND SACRIFICE		1	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	22	13

* INCLUDES AUTOLYZED ANIMALS

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

* U. S. GOVERNMENT PRINTING OFFICE : 1977 241-161/3010